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Synthesis of α-amino phosphonates by diastereoselective addition of diethyl phosphite sodium salt to aldimines derived from Betti base

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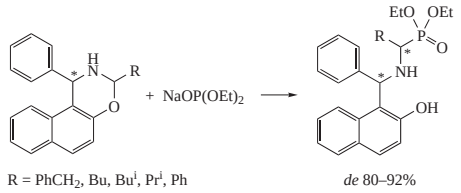
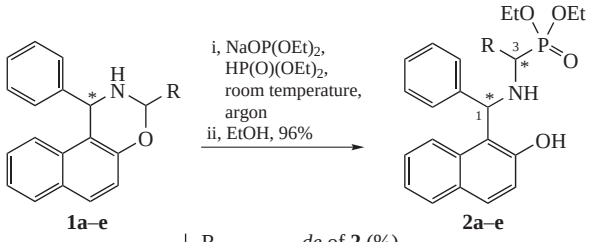
A diastereoselective (*de* 80–92%) synthesis of α-amino phosphonates was accomplished by reaction of diethyl phosphite sodium salt with 3-R-1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*]-[1,3]oxazines being the products of aminoacetalization of aldehydes with 1-(α-aminobenzyl)-2-naphthol (Betti base).



α-Amino phosphonic acids, which are analogues of natural amino acids, exhibit a wide range of biological activity[1] and are used as building blocks for synthesis of physiologically active phosphonopeptides.[1,2] The Pudovik reaction is the most convenient method for their preparing. We have previously reported that the Betti base [1-(α-aminobenzyl)-2-naphthol[3]] is an effective chiral auxiliary for the synthesis of enantiopure α-aminobenzylphosphonates synthesis. Reaction of triethyl phosphite with enantiopure Betti base benzimines (which are in equilibrium with the corresponding 3-aryl-1-phenylnaphthoxazine cyclic forms in solution[4]) in the presence of trifluoroacetic acid affords the target compounds with *de* up to 84%.[5] Mostly, the major diastereomer can be easily separated by crystallization and then transformed to enatiopure α-aminobenzylphosphonic acid by treatment with HCl. However, in living organisms the process of biosynthesis involves exclusively α-aminoalkanecarboxylic acids. Unfortunately, 3-alkyl-1-phenylnaphthoxazines, which are the precursors of α-aminoalkylphosphonates (α-aminoalkanecarboxylic acid analogues), do not react with trialkyl phosphites in the presence of trifluoroacetic acid. We obtained the desired α-aminoalkylphosphonates using halotrimethylsilanes instead of trifluoroacetic acid in the reaction of alkyl-substituted Betti base imines (oxazines) with triethyl phosphite with *de* up to 75%.[6] However, in this case, isolation of major diastereomers caused some difficulties.

Herein, we successfully used diethyl phosphite salts in the reaction with 3-alkyl-1-phenylnaphthoxazines **1a**–**d**. Note that according to the literature[7] reactions of lithium or sodium salts of dialkyl esters of phosphorous acid with imines derived from chiral amines or amides often proceed with high diastereoselectivity.

Reactions of 3-benzyl-, 3-butyl-, 3-isobutyl- and 3-isopropyl-1-phenylnaphthoxazines **1a**–**d** with an excess of diethyl phosphite sodium salt were carried out at room temperature under argon atmosphere, using diethyl phosphite as a solvent (Scheme 1). The reaction mixtures were vigorously stirred for 6 h at room temperature, followed by the addition of 96% ethanol. The volatiles were then removed *in vacuo* and the obtained diastereomeric products were analyzed by NMR.† The ^{1}H and ^{31}P{^{1}H} spectra of these samples in each case contained two sets of α-aminoalkylphosphonates signals, one of which was in a large excess, indicating the high stereoselectivity of the reaction (*de* of 80–90%). Major diastereomers from diastereomeric mixtures **2a** and **2d** were isolated by crystallization from hexane–cyclohexane mixture. Phosphonates **2b** and **2c** were characterized as diastereomeric mixtures.



	R	*de* of **2** (%)
a	$PhCH_2$	90
b	Bu	80
c	Bu^i	82
d	Pr^i	86
e	Ph	92

Scheme 1

Due to the high diastereoselectivity of studied processes it was interesting to test 1,3-diphenylnaphthoxazine **1e** in the same reaction (see Scheme 1). The diastereomeric α-aminobenzylphosphonates **2e** formed had in fact *de* value as 92% which was greater than that (80%) in the case[5] of reaction **1e** + $P(OEt)_3$ + + CF_3CO_2H.

The important point was the relative configurations of chiral centers in resulting amino phosphonates. In our previous work it was established by X-ray single crystal diffraction that reaction **1e** + $P(OEt)_3$ + CF_3CO_2H afforded the major diastereomer with (*RR*/*SS*)-configuration.[5] However, in the reaction **1e** + $P(OEt)_3$ + + $HalSiMe_3$ the major diastereomer **2c** had (*RS*/*SR*)-configuration[6] at C(1) and C(3) chiral centers. Herein, in the reaction **1a**–**e** + + $NaOP(OEt)_2$ the major diastereomers always have (*RR*/*SS*)-configuration.

Comparison of the ^{1}H NMR spectra of the individual diastereomers of these phosphonates with the spectra of the initial

† For details, see Online Supplementary Materials.